Dodecahedrane—The chemical transliteration of Plato's universe (A Review)

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ABSTRACT   The development of chemical interest in three of Plato's five convex polyhedra is described from an historical perspective. The successful synthesis of 1,16-dimethyldodecahedrane and its structural characteristics are outlined. Finally, an account of recent work leading to the still more aesthetically appealing and ultrasymmetric parent dodecahedrane is given.

Men of learning in ancient Greece exhibited particular fondness for, and interest in, five exquisitely symmetric convex polyhedra, each composed of totally equivalent vertices and edges. In Plato's thinking, tetrahedrons constituted the smallest components of the element fire and pentagonal dodecahedra comprised the building blocks of heavenly matter; in between were cubes for earth, octahedra for air, and icosahedra for water. Much later, in the 17th century, the astronomer Johannes Kepler made extraordinary use of these five regular bodies in his model of the universe.

That the heritage of this wonder should inevitably pass into the realm of synthetic organic chemistry comes as no surprise. However, the requisite transliteration into hydrocarbon equivalents necessarily excludes octahedrane and icosahedrane for practical reasons. Of the remaining three, 1 belongs to T_d point group with its 24 identity operations, 2 has full O_h symmetry, and 3, with its I_h character and 120 identity operations, is the

1   2

3
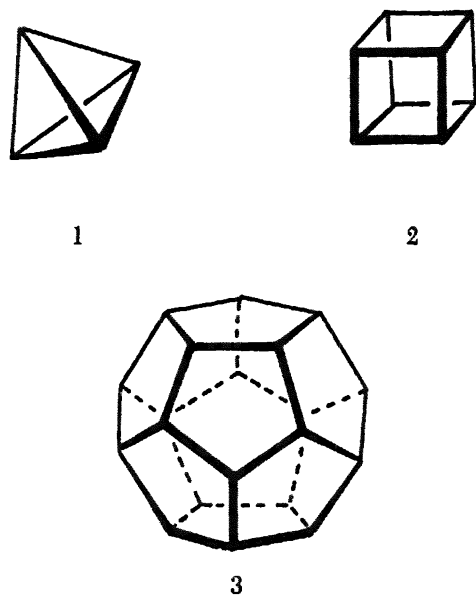
most highly symmetric hydrocarbon possible. All three molecules clearly are structurally unusual, and their properties are not predictable with certainty *a priori* from current theories of chemical bonding. Because the facial angles of tetrahedrane

deviate the greatest from normalcy, this molecule should possess the greatest strain energy per carbon atom. In contrast, dodecahedrane is characterized by minimal angle strain, although unparalleled high levels of torsional strain exist because of the precise eclipsing of all the C-H bonds. The chemist's fascination with 1, 2, and 3 is fueled further by the aesthetically delightful topologies of these structures, the presence of cavities of increasing size (perhaps reaching a practical lower limit in 3), the spectral consequences of 4, 8, or 20 symmetry-equivalent methine units, the absence of structurally allied substances in nature, and much more.

Despite dire theoretical predictions about the intrinsic instability of tetrahedrane, there has been no shortage of attempts to synthesize this fascinating molecule. Although the parent hydrocarbon remains unknown, Maier *et al.* succeeded in 1978 in preparing the tetra-*tert*-butyl derivative 5 (1, 2). The critical steps in the synthesis (Scheme I), which depends very heavily on light-induced reactions, are the photoisomerization and decarbonylation of 4. The colorless crystalline 5 is amazingly resistant to oxygen, moisture, and heat (mp 135°C dec). At the melting temperature, isomerization to tetra-*tert*-butylcyclobutadiene occurs. The extraordinary stability of 5 has been

5   4
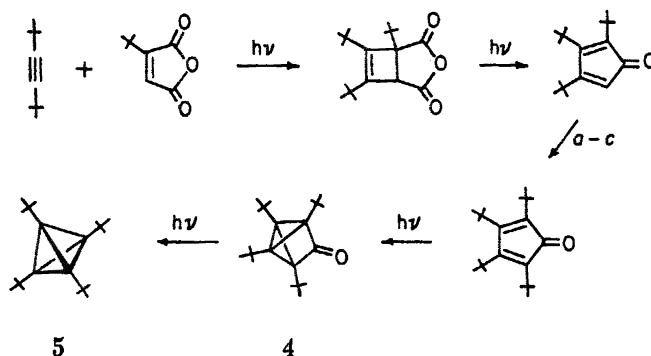
a, Br₂; *b*, KOH; *c*, *tert*-BuLi.
Scheme I

attributed to the fact that rupture of any framework bond is opposed by increased steric interaction between the pendant *tert*-butyl groups. The most notable chemical property of 5 uncovered to date is its penchant for oxidation to the isomerized radical cation in the presence of many reagents.

The tactical elaboration of cubane was masterfully achieved by Eaton and Cole (3) at the University of Chicago as early as 1964. Their protocol (Scheme II) took good advantage of the facility with which 2-bromocyclopentadienone dimerizes to 6. Following photocyclization of the dimer, 2-fold Favorskii ring contraction was achieved with hot potassium hydroxide. Once dicarboxylic acid 7 was in hand, it was a simple matter to remove the carboxyl groups by conventional methods.
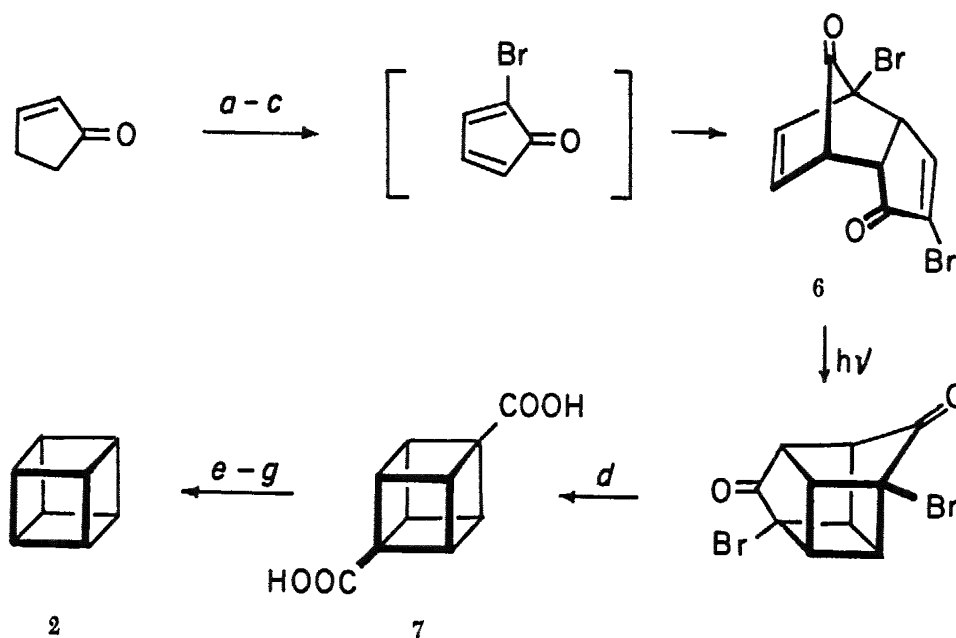
a, NBS; *b*, Br$_2$; *c*, (C$_2$H$_5$)$_3$N; *d*, KOH, H$_2$O, Δ, and then H$_3$O$^+$;
e, SOCl$_2$; *f*, *tert*-BuOOH; *g*, triisopropylbenzene, Δ.

Scheme II

Presumably because of orbital symmetry constraints, **2** is also impressively stable to heat. Only when cubane is kept at 200°C for 2 weeks does one obtain cyclooctatetraene via cuneane (**8**) and semibullvalene (**4**). Silver(I) ion greatly accelerates this particular isomerization (**5**); rhodium(I) leads alternatively to the *syn* dimer of cyclobutadiene (**9**) (**6**, **7**).
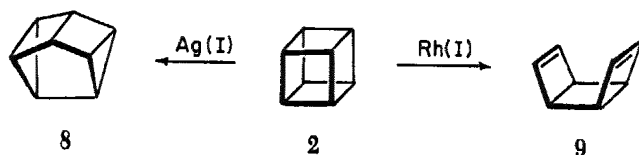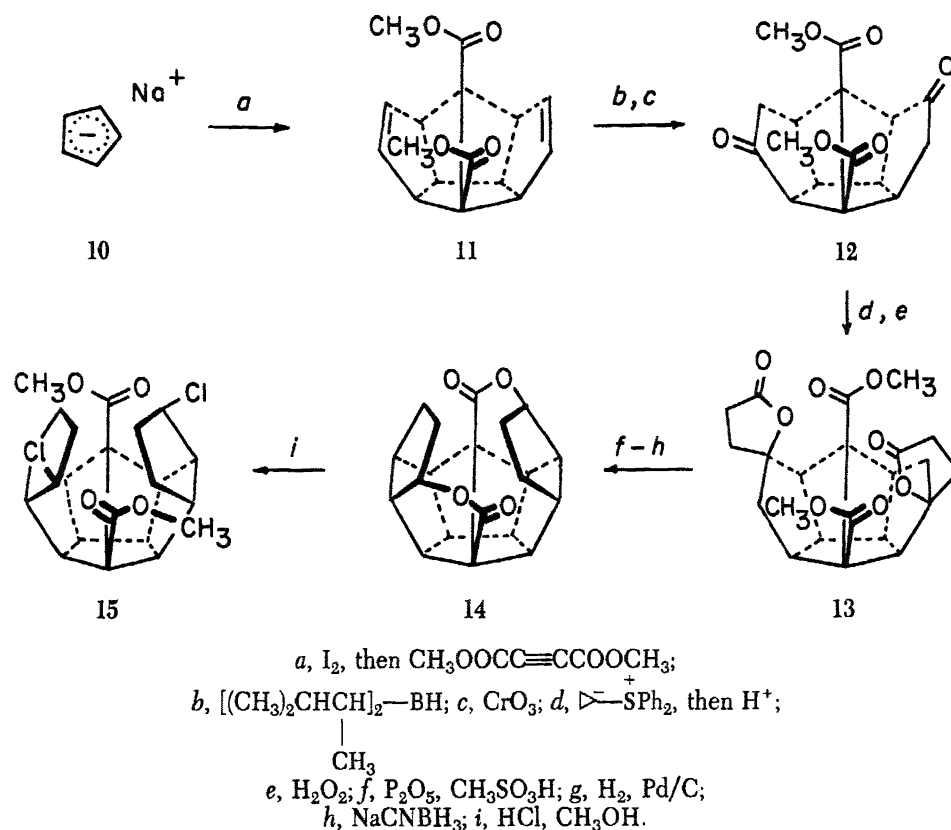

The challenge offered by the synthesis of the pentagonal dodecahedrane is of large proportions. The ultimate objective is to interlink 20 methine units with 30 carbon-carbon bonds in such a way that 12 multiply fused five-membered rings result. Additionally, the topology of **3** is such that all ring fusions are *cis-syn*, a feature which causes many partially constructed precursors to suffer excessively high levels of nonbonded steric strain and consequently to exhibit a pronounced tendency for transannular bonding, framework isomerization, and noncyclopentanoid cyclization (**8**, **9**). It is chiefly for these reasons and other related factors that the several convergent approaches to **3** which have been attempted by various groups have not succeeded as yet. These include the formal combination of two C$_{10}$ units (10–18), capping of a C$_{15}$ unit with a cyclopentane ring (19–22), amalgamation of C$_{16}$-hexaquinacene with a C$_4$ segment (23, 24), and controlled Lewis acid-catalyzed isomerization of a more readily accessible (CH)$_{20}$ isomer (ref. 25; P. von R. Schleyer, personal communication).

These serious complications prompted consideration of a serial synthetic approach to **3**. Importantly, we hoped to overcome the tactical disadvantages of nonconvergency by capitalizing on the symmetry of the target molecule throughout the sequence. Early in 1981, my colleagues and I were pleased to be able to report our successful acquisition of the 1,16-dimethyl derivative (**23**) in a number of steps fewer than the total count of framework

carbon atoms (26–28). From the outset, it was projected that **23** should derive from the cyclopentadienide anion (**10**), a simple and inexpensive commodity. Following oxidative coupling of **10** to 9,10-dihydrofulvalene, a domino Diels–Alder reaction (29–31) is carried out with dimethyl acetylenedicarboxylate to give **11**, a C$_{2v}$-symmetric molecule whose role it is to serve as the cornerstone of the spherical target molecule (Scheme III). Controlled reduction in the symmetry level of this intermediate to provide diketo diester **12** which possesses only a simple C$_2$ molecular axis is entirely possible by a hydroboration-oxidation sequence (32). In practice, however, a somewhat longer, more efficient catercorner oxygenation sequence is preferred (26–28) because the unwanted C$_s$ diketo diester is not produced concomitantly.

Bisspiroannulation of **12** with diphenylcyclopropylsulfonium ylide followed by hydrogen peroxide oxidation delivers the axially symmetric spirolactone **13** which can be isomerized under strongly acidic conditions and subsequently fashioned into dilactone **14**. It must be recognized that the continued maintenance of C$_2$ symmetry now reduces our analysis of the subsequent chemistry of **14** to the manipulation of a pair of symmetry-related ester carbonyl groups. Furthermore, this intermediate already contains all requisite 20 carbon atoms and has 12 of the all-important *cis*-locked methine stereocenters properly installed. Although the chemical reactivity of **14** proved far less controllable than originally anticipated (33, 34), the pivotal conversion to **15** can be accomplished quite efficiently.

Having arrived at **15** in a minimum of nine laboratory steps, we required an equal number to craft the monoseco alcohol **20** (Scheme IV). Under the influence of lithium in liquid ammonia, **15** experiences a splendid reduction-alkylation sequence to generate a dienolate which is directly methylated to yield **16** (35). In this way, the endo orientation of the pair of carbonyl groups is guaranteed and the methyl substituents serve as invaluable ^{1}H NMR beacons. Light-induced ring closure at the ketone site (ester groups are generally photoinactivatable), dehydration of the resulting tertiary alcohol, and diimide reduction delivers the triseco ester **17**. While this intermediate clearly possesses

a, I₂, then CH₃OOCC≡CCOOCH₃;

b, [(CH₃)₂CHCH]₂—BH; *c*, CrO₃; *d*, ▷⁺—SPh₂, then H⁺;
            |
           CH₃

e, H₂O₂; *f*, P₂O₅, CH₃SO₃H; *g*, H₂, Pd/C;
h, NaCNBH₃; *i*, HCl, CH₃OH.

Scheme III

many of the desirable structural features being sought, its op-
posed methylene groups remain unfunctionalized. After some
preliminary studies, the decision was made to address this po-
tentially complex issue at a later stage. Following reduction of
17 to the aldehyde level, 18 was photocyclized as before. The

efficiency of this process was appreciably lower (29%) than here-
tofore because of the well-established tendency of tertiary al-
dehydes to experience decarbonylation from their excited
states. Nevertheless, the important point here is that a five-ring
ketone (19) is produced upon which light may be impinged for

a, Li/NH₃, then CH₃I; *b*, h*ν*; *c*, TsOH, C₆H₆, *d*, HN=NH,
    CH₃OH; *e*, (*i*-Bu)₂AlH; *f*, PCC, CH₂Cl₂.
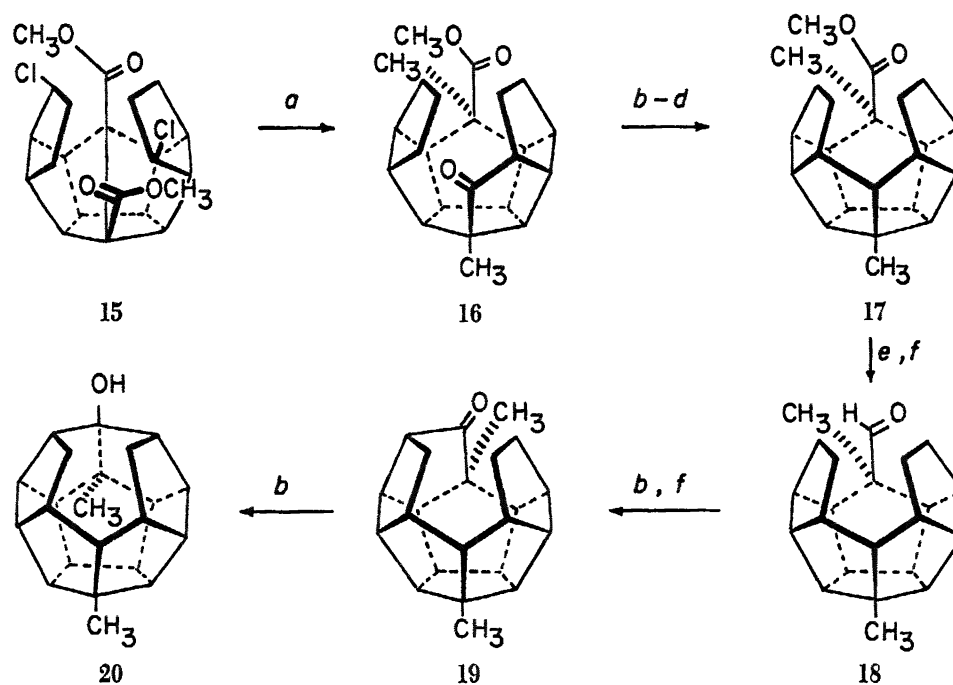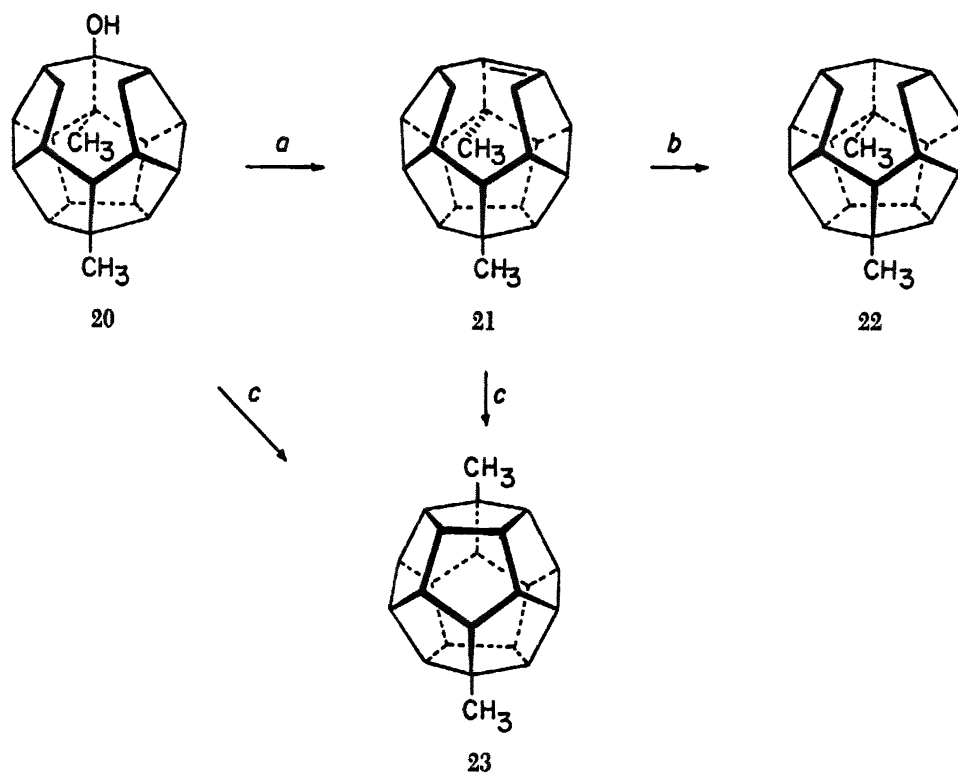
Scheme IV

a, TsOH, C_6H_6; b, H_2NNH_2, H_2O_2; c, CF_3SO_3H, CH_2Cl_2.

Scheme V

the third time. Closure to the monosecododecahedral alcohol 20 proved to be encouragingly simple and efficient, despite the extreme steric congestion which develops in the gap and exerts major geometric alterations in the superstructure as a whole (26–28).

With arrival at 20, it proved an easy matter to proceed to the beautifully crystalline hydrocarbon 22 which possesses an eight-line ^{13}C NMR spectrum due to a return to C_{2v} symmetry. Both 20 and 21 could be cyclized under extreme acid conditions to

the disubstituted D_{3d}-symmetric dodecahedrane 23. The unexpected occurrence of a 1,2-methyl migration during this installation of the final framework bond was substantiated by ^{1}H and ^{13}C NMR (merely four carbon resonances) as well as x-ray crystallography. Some of the more unique physical properties of 23 include its reluctance to melt (discoloration begins above 350°C), its density (1.412 g/cm³), its relatively small transcavity distance (0.9 Å), and its marked resistance to fragmentation in the mass spectrometer.


Scheme VI

Review: Paquette

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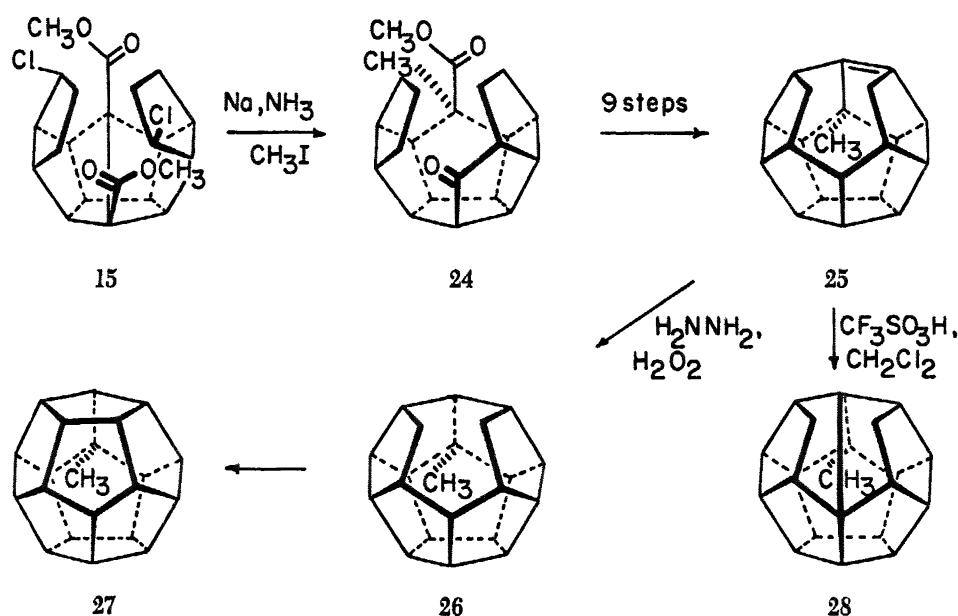
The situation at this point was such as to make pursuit of the parent $(CH)_{20}$ hydrocarbon irresistable. Utilization of **23** as a serviceable precursor was not viewed favorably because of the inoperability of Schleyer's catalyst systems (**36–37**) under the high-vacuum conditions necessary for its volatilization (D. W. Balogh, personal communication) and the unlikely workability of chemospecific methyl oxidation and ensuing decarboxylation in this instance (**38**). Furthermore, the entire synthetic sequence would be protracted by the inclusion of these additional proposed transformations. As a result, we sought to adapt the synthesis just described in as efficient a manner as possible.

Highly pertinent to this end was our eventual discovery of a method for transforming dichloro diester **15** into monoalkylated keto ester **24** by strict control of the amount of methyl iodide. Equally encouraging was the expeditious manner in which methylsecododecahedrane (**26**) was fashioned from this intermediate (Scheme VI). However, it was noted in the course of this study that treatment of **25** with trifluoromethanesulfonic acid in dichloromethane as before resulted in isomerization to a complex mixture of several hydrocarbons among which **27** was clearly not dominant (R. J. Ternansky, personal communication). By careful repeated recrystallization, the major constituent was obtained in a pure state and identified as the "isododecahedrane" **28** by x-ray crystal structure analysis (G. G. Christoph, personal communication). Evidently, the substantial steric compression present in the protonated form of **25** is more than adequate to foster a most remarkable transannular electrophilic substitution with inversion of configuration! To eliminate this reaction channel, the fully saturated seco hydrocarbon was prepared and subjected to dehydrogenation over palladium on charcoal. The best conditions uncovered to this time appear to produce **27** admixed with other equally nonpolar materials (R. J. Ternansky, personal communication). At present, we are actively engaged in enhancing the proportion of **27** in these mixtures and in isolating this substance in pure form.
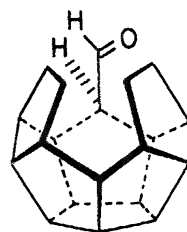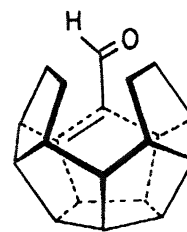

29   **30**

At about the same time, we succeeded in preparing aldehyde **29**. To our disappointment, this substance has proven to be too sensitive to deal with on a preparative scale, being remarkably prone to oxidative dehydrogenation and conversion to **30**, presumably as a direct consequence of its high enol content. Suitable resolution of this difficulty has mandated the introduction of a blocking group whose appropriateness was to be dictated by its inertness toward several reagents (including light) and its ready removal at a later stage.

As matters worked out, our first attempt in this direction was successful, use of chloromethyl phenyl ether as the electrophile providing convenient access to **31**. As shown in Scheme VII, the phenoxymethyl side chain causes no interference during the three-step "stitching together" of the other side of the sphere. Nor does it become entangled with proximate reactive functional groups as **32** is modified to the aldehyde level and subjected to photochemical cyclization. Sequential Birch reduction, acid hydrolysis, and pyridinium chlorochromate oxidation of **33** proceed to make keto aldehyde **34** cleanly available. This intermediate, which is seen to be a β-keto aldehyde, conforms to the susceptibility of this class of compounds to retroaldol cleavage in alkaline solution. Since the monoseco olefin derived from **35**, like **25**, is prone to uncontrolled carbocationic rearrangement, its diimide reduction was effected. When recourse


31   **32**   **33**

36   **35**   **34**
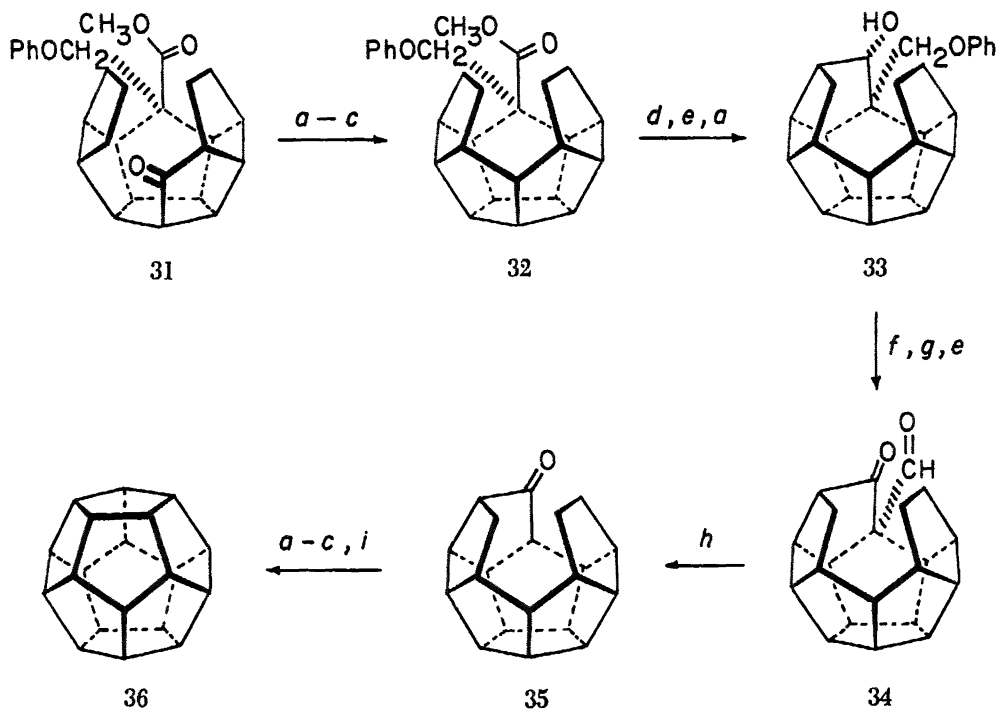
a, hν; b, TsOH, C_6H_6; c, NH_2NH_2, H_2O_2; d, (i-Bu)₂AlH; e, PCC, CH_2Cl_2; f, Li, NH_3, C_2H_5OH; g, HCl, H_2O, THF; h, KOH, H_2O, C_2H_5OH; i, 10% Pd-C, 250°C.

Scheme VII

is made to catalytic dehydrogenation of the resulting secododecahedrane, a mixture of compounds containing the desired 36 is produced. Although this drawback makes isolation of dodecahedrane difficult, this accomplishment has recently been achieved (R. J. Ternansky, personal communication). Due to severely limited quantities of 36 at this time, our study of its properties has not yet progressed far. Nonetheless, the expectation that its ^{1}H (δ 3.35 in CDCl$_3$) and ^{13}C (66.93 ppm in CDCl$_3$) spectra should be characterized by lone singlets has been borne out.

Predictions concerning dodecahedrane abound (39–46). As our synthetic approach becomes more streamlined and reasonable quantities of this hydrocarbon become available, we shall explore the preparation of its amino derivative (a potential antiviral and anti-parkinsonism agent) and carbocation (a stable, highly fluxional species?), as well as its conversion to dodecahedrene (a highly distorted cyclic olefin). In addition, it is anticipated that several intermediates in our synthetic scheme might be successfully deployed to arrive at azadodecahedrane and the homododecahedryl cation [a totally degenerate (CH)$_{21}^+$ species?]. Attention shall also be given to the possibility of enlarging the cavity by supplanting select symmetrically dis-
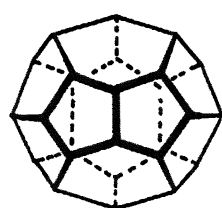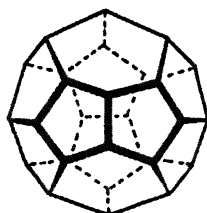
37   38

posed cyclopentane rings with larger six-membered ones as in pentakaidecahedrane (37) and hexakaidecahedrane (38). With these hydrocarbons in hand, the possibility of sealing an atom such as helium in the interior becomes more realistic.

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